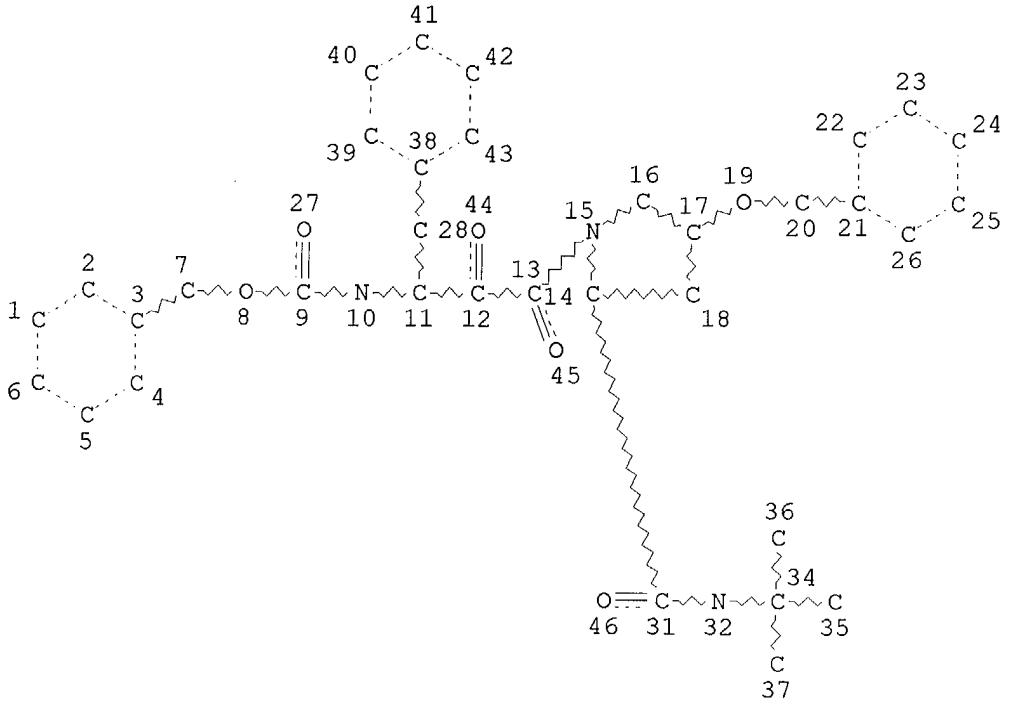
=> d que
L2 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 43

STEREO ATTRIBUTES: NONE
L4 9 SEA FILE=REGISTRY SSS FUL L2
L5 3 SEA FILE=HCAPLUS ABB=ON PLU=ON L4

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L5 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:801933 HCAPLUS
DOCUMENT NUMBER: 137:226
TITLE: A study on docking mode of HIV protease and their inhibitors
AUTHOR(S): Akaho, Eiichi; Morris, Garret; Goodsell, David; Wong, David; Olson, Arthur
CORPORATE SOURCE: Fac. Pharmacetuical Sci., Kobe Gakuin Univ., 518 Arise, Ikawadani-cho, Nishi-ku, Kobe, 651-2180, Japan
SOURCE: Journal of Chemical Software (2001), 7(3), 103-114
CODEN: CHSFEC; ISSN: 0918-0761
PUBLISHER: Kagaku Sofutowea Gakkai
DOCUMENT TYPE: Journal

LANGUAGE: English

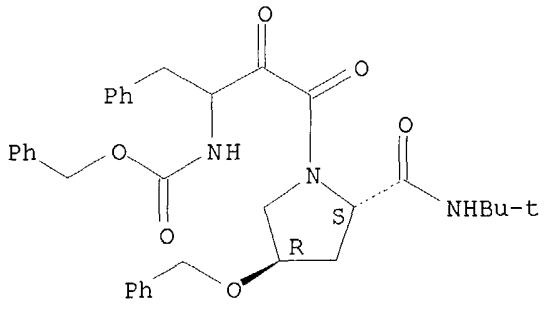
AB The capability to propose feasible ways of binding a putative ligand inhibitor to a known receptor site is crucial to the successful structure-based drug design. A computer docking approach is to position or "dock" ligand and receptor mols. together in many different ways and then score each orientation by applying a reasonable evaluation function. AutoDock3.0 is an unbiased type docking program in which a user does not have to direct a ligand to an active site, but the system finds an optimal position after a ligand is placed in a random manner. Synthesized derivs. of the intact inhibitor (inh1) of HIV protease were investigated for their docking modes as compared with their Ki values. Among the derivs., inh3trans and inh6H were found to be more powerful inhibitors of HIV protease than the others. Gibbs free energy calculated by applying mol. mechanics interaction energies was compared with the one obtained by using exptl. inhibitory potencies for a series of HIV protease inhibitors, and a fairly good correlation was found between the two. Based on this favorable correlationship between the computational and the exptl. results, the computational expts. were pursued for the compds. drawn by Sybyl taking into consideration the fact that unexploited carbon affinity regions (or hydrophobic regions) with sizable volume were detected on the docking study of inh1 and inh8 against HIV protease. Those were compds. with a t-Bu substituted by various hydrophobic side chains. Among those a compound with a benzyl group exhibited the lowest docking energy. Since one of the goals of this paper was to perform the computational drug-design experiment to investigate potential HIV protease inhibitors, the authors would like to leave the clin. investigational work for the expertise of those areas.

IT **191850-29-0 433709-65-0**
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(docking mode of HIV protease and their inhibitors)

RN 191850-29-0 HCAPLUS

CN Carbamic acid, [3-[(2S,4R)-2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

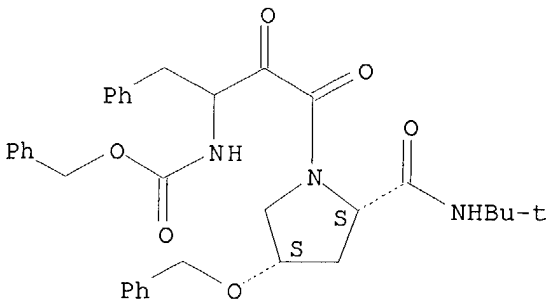


RN 433709-65-0 HCAPLUS

CN Carbamic acid, [3-[(2S,4S)-2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Searched by P. Ruppel



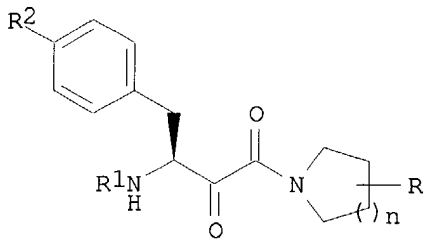
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:473732 HCAPLUS
DOCUMENT NUMBER: 127:81793
TITLE: Preparation of hydroxyethylamine core structures as HIV and FIV protease inhibitors
INVENTOR(S): Wong, Chi-Huey; Slee, Deborah H.; Laslo, Karen
PATENT ASSIGNEE(S): Scripps Research Institute, USA; Wong, Chi-Huey; Slee, Deborah H.; Laslo, Karen
SOURCE: PCT Int. Appl., 202 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9721100	A1	19970612	WO 1996-US19571	19961209
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2238337	AA	19970612	CA 1996-2238337	19961209
AU 9712844	A1	19970627	AU 1997-12844	19961209
AU 728373	B2	20010111		
EP 873519	A1	19981028	EP 1996-943657	19961209
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2000502332	T2	20000229	JP 1997-521485	19961209

PRIORITY APPLN. INFO.: US 1995-568532 A2 19951207
WO 1996-US19571 W 19961209

OTHER SOURCE(S): MARPAT 127:81793
GI



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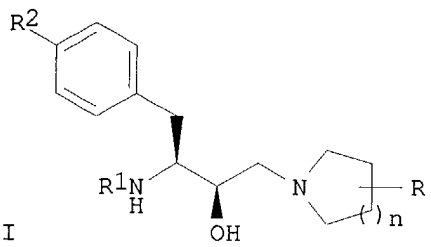
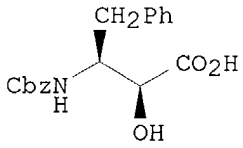
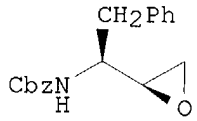


II



III



IV

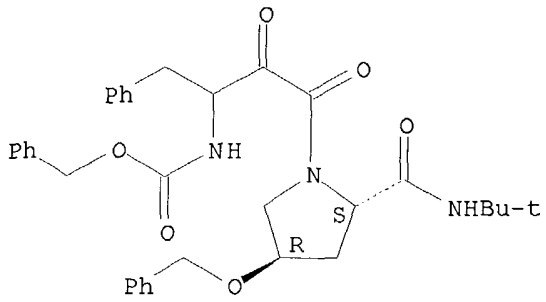
AB Combinatorial libraries of HIV and FIV protease inhibitors are characterized by α-keto amide or hydroxyethylamine core structures I and II [n = 1, 2; R = one or more groups CONHCMe3, CH2OH, CH2OMe, CH2OCH2Ph, OH, OCH2Ph, C1-4 alkoxy, optionally nitro-substituted 2-, 3-, or 4-MeOC6H4CH2O, 2,3- or 3,4-methylenedioxyphenylmethoxy, etc.; R1 = PhCH2O2C (Cbz), Me3CO2C (Boc), acyl; R2 = H, HO, PhCH2O, C1-4 alkoxy, optionally nitro-substituted 2-, 3-, or 4-MeOC6H4CH2O, 2,3- or 3,4-methylenedioxyphenylmethoxy] flanked by on one side by substituted pyrrolidines, piperidines, or azasugars and on the other side by Phe, Tyr, or substituted tyrosines. The libraries are synthesized via coupling of the nitrogen heterocycles with hydroxy acids, e.g. III, followed by oxidation to the keto amide, or a one-step coupling with epoxides, e.g. IV. Highly efficacious drug candidates are identified by screening the libraries for binding and inhibitory activity against both HIV and FIV protease. Drug candidates displaying clin. useful activity against both HIV and FIV protease are identified as being potentially resistive against a loss of inhibitory activity due to development of resistant strains of HIV.

IT **191850-29-0P 191850-31-4P 191850-60-9P**
191851-40-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of hydroxyethylamine core structures as HIV and FIV protease inhibitors)

RN 191850-29-0 HCAPLUS

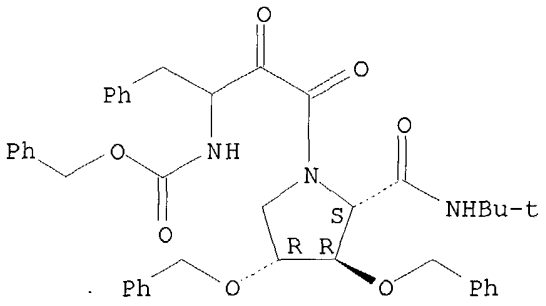
CN Carbamic acid, [3-[(2S,4R)-2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



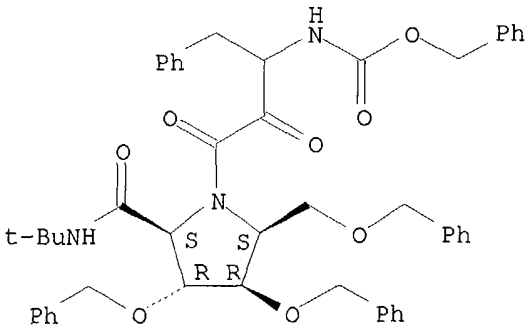
RN 191850-31-4 HCAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3,4-bis(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2α,3β,4α)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 191850-60-9 HCAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3,4-bis(phenylmethoxy)-5-[(phenylmethoxy)methyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2α,3β,4α,5α)]-[partial]- (9CI) (CA INDEX NAME)

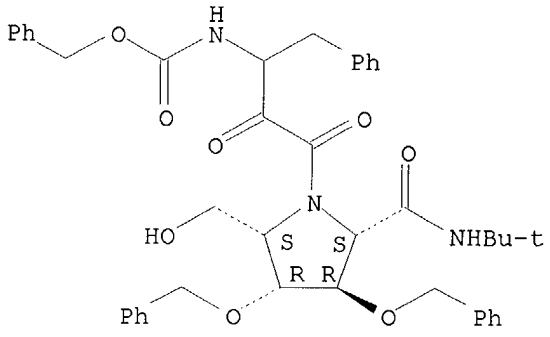
Absolute stereochemistry.



RN 191851-40-8 HCAPLUS

CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-5-(hydroxymethyl)-3,4-bis(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2α,3β,4α,5α)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1995:938815 HCAPLUS
DOCUMENT NUMBER: 124:105570
TITLE: Selectivity in the Inhibition of HIV and FIV Protease: Inhibitory and Mechanistic Studies of Pyrrolidine-Containing α-Keto Amide and Hydroxyethylamine Core Structures
AUTHOR(S): Slee, Deborah H.; Laslo, Karen L.; Elder, John H.; Ollmann, Ian R.; Gustchina, Alla; Kervinen, Jukka; Zdanov, Alexander; Wlodawer, Alexander; Wong, Chi-Huey
CORPORATE SOURCE: Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of the American Chemical Society (1995), 117(48), 11867-78
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study describes the development of new pyrrolidine-containing α-keto amide and hydroxyethylamine core structures as mechanism based inhibitors of the HIV and FIV proteases. The α-keto amide core structure is approx. 300-fold better than the corresponding hydroxyethylamine isosteric structure and 1300-fold better than the corresponding phosphinic acid derivative as an inhibitor of the HIV protease. The α-keto amide is however not hydrated until it is bound to the HIV protease as indicated by the NMR study and the x-ray structural anal. Further anal. of the inhibition activities of hydroxyethylamine isosteres containing modified pyrrolidine derivs. revealed that a cis-methoxy group at C-4 of the pyrrolidine would improve the binding 5- and 25-fold for the trans-isomer. Of the core structures prepared as inhibitors of the HIV protease, none show significant inhibitory activity against the mechanistically identical FIV protease, and addnl. complementary groups are needed to improve inhibition.

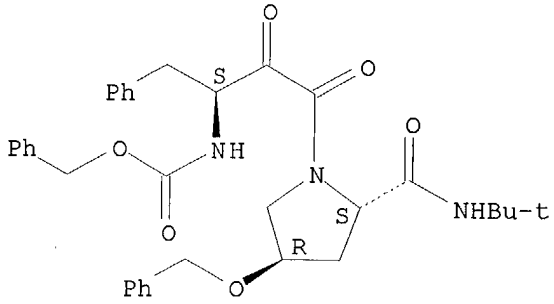
IT **172696-34-3P 172823-22-2P 172823-24-4P 172823-25-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(reaction with benzyloxycarbonyl chloride)

RN 172696-34-3 HCAPLUS

CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-[1(R*),2α,4β]]- (9CI) (CA INDEX NAME)

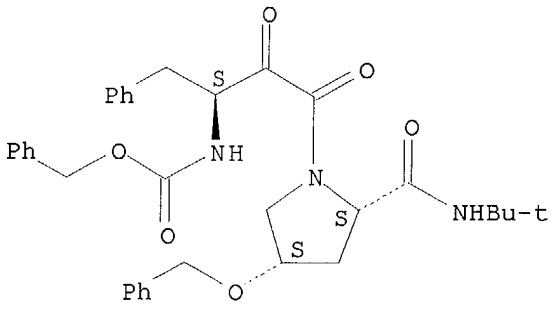
Absolute stereochemistry.



RN 172823-22-2 HCAPLUS

CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-[1(R*),2α,4α]]- (9CI) (CA INDEX NAME)

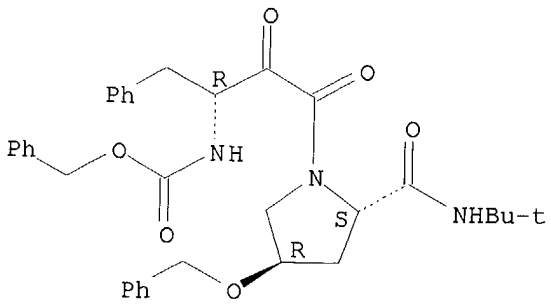
Absolute stereochemistry.



RN 172823-24-4 HCAPLUS

CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-[1(S*),2α,4β]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 172823-25-5 HCAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-[1(S*),2α,4α]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.